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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,769	10/25/2000	Darwin J Prockop	9598-101U2(99-0356)	4022

7590 08/10/2004

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EXAMINER

SHUKLA, RAM R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant(s)

PROCKOP ET AL.

Art Unit

1632

Period for Reply

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1) ☒ Responsive to communication(s) filed on 21 May 2004.

2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

4) ☒ Claim(s) 1-29 and 31-36 is/are pending in the application.

4a) Of the above claim(s) is/are withdrawn from consideration.

5) ☐ Claim(s) is/are allowed.

6) ☒ Claim(s) 1-29 and 31-36 is/are rejected.

7) ☐ Claim(s) is/are objected to.

8) ☐ Claim(s) are subject to restriction and/or election requirement.

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7062

4) ☐ Interview Summary (PTO-413) Paper No(s). _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5-21-2004 has been entered.
2. Claims 1-29 and 31-36 are under consideration.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claim 1-29 and 31-36 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Huang et al (Biotechnology Letters, 19:89-92, 1997).

Huang et al teaches cell density-dependent proliferation of the murine bone marrow-derived stromal cell lines. The art teaches to isolate marrow cells and their culture. The art teaches to culture cells at a 3 day interval by serial culture and then plating them in 96-well plates by seeding the cells at 5, 50 and 500 cells per well that would amount to 2-7 cells per centimeter square (see the second paragraph in the left column on page 90). The art also teaches culturing cells in the presence of conditioned medium to test the effect of conditioned medium on the proliferation of stromal cell lines (see the last paragraph in the right column on page 91).

It is noted that different claims add one more replating step (such as claim 12 or 16) which is inherently present in cell culture methods where cells are cultured for several rounds to either maintain them in culture or for preparing new cell lines or for starting new cultures from a source, such as from tissue samples, cloning of a single cell etc. Additionally, the claimed invention is a general method of culturing cells at low density of 50 cells per centimeter square or lower than that and does not recite any specific embodiment that would make it distinct from the prior art of record.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1, 22-29 and 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al (Biotechnology Letters, 19:89-92, 1997), Kuznetsov et al, Azizi et al, Greenberger et al (US Patent No 5,766,950, 6-16-1998) and Prockop (Science 276:71-74, 1997).

Art Unit: 1632

Huang et al teaches cell density-dependent proliferation of the murine bone marrow-derived stromal cell lines. The art teaches to isolate marrow cells and their culture. The art teaches to culture cells at a 3 day interval by serial culture and then plating them in 96-well plates by seeding the cells at 5, 50 and 500 cells per well that would amount to 2-7 cells per centimeter square (see the second paragraph in the left column on page 90). The art also teaches culturing cells in the presence of conditioned medium to test the effect of conditioned medium on the proliferation of stromal cell lines (see the last paragraph in the right column on page 91).

Kuznetsov et al teach single colony derived strains of human marrow stromal fibroblasts (HMSF) cells. Second paragraph in the left column of page 1337 teaches the method of singly colony derived HMSF which comprising plating cells at $0.14-1.4 \times 10^3$ cells/cm² or $0.007-3.5 \times 10^3$ cells/cm². The art also teaches multiple passaging and cell culture medium comprised fetal bovine serum (see the last paragraph in the right column on page 1336). This art does not teach to add a growth factor to the culture medium for growing human marrow stromal cells.

Azizi et al teaches growing of human marrow stromal cells and addition of PDGF-AA to the culture (see figure 1 and the first paragraph of the results section on page 3910 continued on page 3911).

Greenberger teaches a method for selection and expansion of stromal cells, wherein the cells are grown in a vessel pre-coated with fibroblast growth factor and the cell culture is maintained in the presence of conditioned medium (see lines 1-51 in column 6).

Prockop reviews the state of the art of marrow stromal cells, their isolation, characteristics, and growth properties in cell culture. For example, these cells secrete cytokines and growth factors, such as IL-1, IL-6, CSF-1, CSF (see the right column on page 72).

At the time of the invention, an artisan of skill would have been motivated to add growth factors and conditioned medium from stromal cells to the culture medium of human stromal cells with a reasonable expectation of success, since it was routine in the art to add conditioned medium to stromal cell culture. An artisan

would have been motivated to add conditioned medium to the culture because the medium contains growth factors and cytokines that are helpful in the growth of marrow stromal cells. It would be logical to add the condition medium from cells that are similar in density for maintaining the culture conditions and for testing the presence of potential growth factors in the conditioned medium. Regarding the limitations of the molecular weight of the factors, it is noted that the cytokines and growth factors secreted by marrow stromal cells would be in the range of molecular weight recited. Regarding the limitation of colony forming unit as the assay to compare the viability and expandability of the cells, it is noted that it was routine at the time of the claimed invention to use colony forming assay or growing single cell colonies and expand them in vitro to develop cell lines and also for studies. Furthermore, it was routine in the art to compare growth of control cells with that of treated cells for assessing the effect of growth factors on growth of marrow stromal cells, for example, see Azizi et al (figure 1) or Huang et al (growth factors present in the conditioned medium, see figure 2).

7. Applicant's arguments with respect to claims 1-29 and 31-26 have been considered but are moot in view of the new ground(s) of rejection.


8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Art Unit: 1632

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER